

DOCKET NO.: CP380C  
Application No.: 10/649,776  
Office Action Dated: December 15, 2005

PATENT

## REMARKS

Following entry of the foregoing amendments, claims 1 and 3 to 10 will be pending in the application. Claims 3, 7, and 8 have been amended, and claims 2 and 11 have been canceled, herein, without prejudice. No new claims have been added. Support for the amendments is found throughout the specification as originally filed. No new matter has been added.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

**Alleged Obviousness**

Claims 1 to 11 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chinese Patent number CN 1079391 ("the 391 patent") in view of U.S. Patent No. 6,720,011 ("the Zhang patent") and Shimotsuura, S., *Journal of Tokyo Dental College Society*, 1986, 86(8) 1237-1253 ("the Shimotsuura article"). Applicants respectfully request reconsideration and withdrawal of the rejection because the office action has failed to establish *prima facie* obviousness.

To establish *prima facie* obviousness, the Patent Office must provide objective evidence that the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, contains some suggestion or incentive that would have motivated those of ordinary skill in the art to modify a reference or to combine references. *In re Lee*, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002); *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1998). And the proposed modification or combination of the prior art ***must have had a reasonable expectation of success***, determined from the vantage point of those of ordinary skill in the art, at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

"[W]hether a particular combination might be 'obvious to try' is not a legitimate test of patentability." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). "Obvious to try" situations arise where it might have been obvious to "explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re*

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*O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). See also *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.ed. 1367, 1380 (Fed. Cir. 1986)(stating that "At most, these articles are invitations to try monoclonal antibodies in immunoassays but do not suggest how that end might be accomplished.")(emphasis in original).

Upon review of the references cited in the Office action, those skilled in the art would not have reasonably expected at the time of the invention that arsenic trioxide could have been successfully used to treat melanoma in humans. At most, it might have been obvious to persons skilled in the art *to try* to use arsenic trioxide to treat melanoma, but much more is required to establish *prima facie* obviousness.

The 391 patent describes the treatment of "skin cancer" and "body surface tumors" with a combination of arsenic trioxide and traditional Chinese medicines. As pointed out in the Office action, the patent does not describe treatment of *melanoma* with arsenic trioxide, however.<sup>1</sup>

The Zhang patent describes arsenic trioxide compositions<sup>2</sup>, but fails to provide any guidance whatsoever as to the efficacy of the compositions for melanoma treatment. The patent's single working example describes the use of arsenic trioxide compositions for the treatment of a particular type of leukemia (acute promyelocytic leukemia) (col. 2, ln. 59 to col. 3, ln. 27). In addition, the patent's description of the effect of the described arsenic trioxide compositions on cancer cells is limited to a description of its effect on leukemia cells:

Laboratory experiments indicate that the composition shows a strong abruptive effect on the membranes of leukemic cells. It also inhibits DNA/RNA synthesis in such cells, reduces the rate of proliferation of leukemic cells and destroys the leukemic cells.

(col. 2, lns. 23 to 27).

The Shimotsuura article describes the efficacy of arsenic trioxide in a mouse sarcoma model and indicates that arsenic trioxide was only efficacious when it was coadministered with an antidote. The article fails to describe or suggest the treatment of melanoma with arsenic trioxide. Although the Office action asserts that the article teaches that "antineoplastic [*sic*]

<sup>1</sup> Office action dated December 15, 2005, page 3.

<sup>2</sup> "The present invention is directed to an intravenous drip composition for the treatment of cancers. The cancers treatable include leukemia, hepatoma and lymphoma." (col. 1, lns. 33 to 35).

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actions of arsenic trioxide are primarily achieved by DNA composition blockage,"<sup>3</sup> the article states that the DNA composition blockage occurred in the S-180 (sarcoma) cells transplanted into the mice, and does not teach that DNA composition blockage occurs in cancerous cells other than sarcoma cells:

From above results,  $\text{As}_2\text{O}_3$  is considered that can increase life span of the mouse by blocking DNA composition of S-180 cells and protein composition.<sup>4</sup>

The references cited in the Office action thus fail to teach or suggest that arsenic trioxide can be successfully used to treat melanoma in humans. Rather, the references teach that arsenic trioxide has been used in humans to treat unspecified "skin cancer" and acute promyelocytic leukemia and suggest that it may be effective against sarcomas when administered in conjunction with an antidote.

As understood by those skilled in the art at the time of the invention, there are many different types of skin cancer, and different approaches are taken towards treating different types of skin cancer. For example, the most common types of skin cancer are basal cell carcinoma and squamous cell carcinoma.<sup>5</sup> Other types of skin cancer include melanoma, cutaneous T-cell lymphomas, Kaposi's sarcoma, extramammary Paget's disease, apocrine carcinoma of the skin, and metastatic malignancies from various primary sites.<sup>6</sup> Those skilled in the art would have appreciated at the time of the invention that the efficacy of a particular anti-cancer agent against a specific type of cancer was not predictive of its efficacy against other types of cancers. It was understood that "[i]ncreasingly disease-specific therapies are being developed that will have optimum application for only one tumor type, although representing ineffective and toxic treatment for others."<sup>7</sup> Indeed, the therapeutic agents most commonly used to treat cancers at the time of the invention (and at present, as well) were effective only against specific types of cancers, and generally did not exhibit broad efficacy against numerous cancer types.<sup>8</sup> Accordingly, those skilled in the art would not have reasonably expected that arsenic trioxide

<sup>3</sup> Office action dated December 15, 2005, page 3.

<sup>4</sup> Page 20 of the English translation.

<sup>5</sup> National Cancer Institute Website (copy enclosed as Exhibit A).

<sup>6</sup> *Id.*

<sup>7</sup> *Medical Oncology*, Calabresi, P., et al., eds., 1985, Macmillan Publishing Company, page 257 (copy enclosed as Exhibit B).

<sup>8</sup> *Id.* at 295-297 (copy enclosed as Exhibit B.)

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could have been successfully used to treat melanoma in humans just because it had been reported to have efficacy against an unspecified type of skin cancer. Although those skilled in the art might arguably have considered trying to use arsenic trioxide to treat melanoma, the results of doing so could not have been predicted with a reasonable degree of certainty. Accordingly, those skilled in the art at the time of the invention would not have reasonably expected that arsenic trioxide could have been successfully used to treat melanoma in humans.

The Office action asserts that “[b]ecause melanoma is an uncontrolled growth of cells, one having ordinary skill in the art would have been motivated to administer arsenic trioxide to treat such uncontrolled growth of cells, particularly in view of its adverse effect on rapid DNA replication.”<sup>9</sup> However, as discussed above, even if those skilled in the art would have been so motivated, they would not have had a reasonable expectation of success for such an endeavor. The Office action appears to be asserting that those skilled in the art would have been motivated to use arsenic trioxide to treat any type of uncontrolled cell growth. Due to the nature of cancer, and methods for its treatment and management at the time of the invention, however, those skilled in the art would not have reasonably expected that an agent shown to be effective against an unspecified type of skin cancer could have been successfully used to treat melanoma in humans. As discussed above, there are many types of skin cancers, and different approaches have been taken for treating different types of skin cancers. For example, the most common types of skin cancer, basal cell carcinoma and squamous cell carcinoma, are treated by topical application of 5-fluorouracil.<sup>10</sup> In contrast, melanoma is not typically treated by topical application of a chemotherapeutic, but is treated by systemic administration of carmustine, dacarbazine, interferon- $\alpha$ , or hydroxyurea.<sup>11</sup> Different types of skin cancers are thus treated differently, and the reported use of arsenic trioxide to treat unspecified “skin cancer” would not have led those skilled in the art to reasonably believe that melanoma could have been successfully treated with arsenic trioxide.

<sup>9</sup> Office action dated November 18, 2005, page 4.

<sup>10</sup> National Cancer Institute Website (copy enclosed as Exhibit C).

<sup>11</sup> *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, Ninth Edition, Hardman J.G., et al., eds., 1996, McGraw-Hill, page 1227 (copy enclosed as Exhibit D).

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Applicants respectfully submit, therefore, that the Office action has failed to establish *prima facie* obviousness, and Applicants, accordingly, respectfully request withdrawal of the rejection.

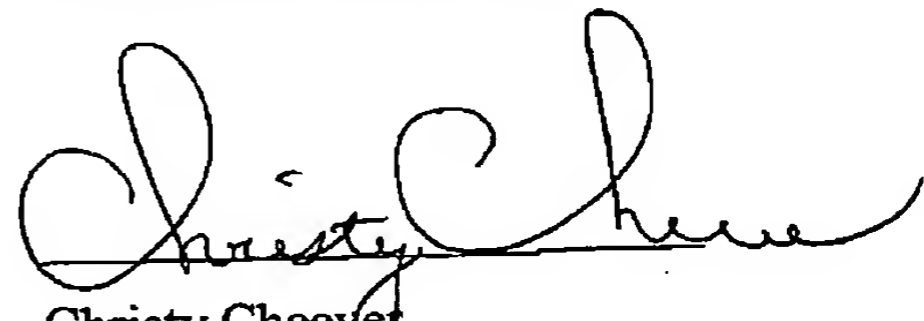
**Information Disclosure Statement**

In response to the Examiner's request for clarification as to which of the search reports cited in the Form PTO 1449 was issued in connection with the corresponding European application, the "International Search Report of EP 03019629"<sup>12</sup> was issued in connection with the counterpart European application.

**Conclusion**

Applicants believe that the foregoing constitutes a complete and full response to the Office action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,



Christy Cheever  
Registration No. 52,722

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CEPHALON, Inc.  
41 Moores Road  
PO Box 4011  
Frazer, PA 19355  
Telephone: 610-833-5743  
Telefax: 610-727-7651

<sup>12</sup> The Form PTO 1449 incorrectly states that the application number of the corresponding European application is "EP 03019628."